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SHORT COMMUNICATIONS

Reaction of 5,5-Dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles with Alcohols

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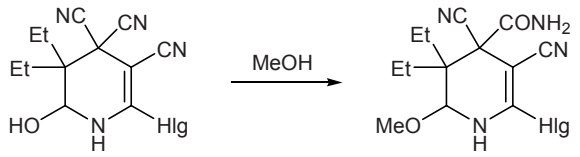
We previously reported that 2-halo-6-hydroxy-5,5-dimethyl-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles **I** in methanol undergo transformation involving replacement of the hydroxy group and mild intramolecular hydrolysis of one cyano group [1]. It was also noted that such transformation is determined by structural specificity of the substrates which possess a hemiaminal fragment and spatially close axial hydroxy and cyano groups [1, 2]. While continuing studies in this line we found that tetrahydropyridines **Ia** and **Ib** react with methanol in anhydrous acetonitrile in a similar way, leading to 6-halo-4,5-dicyano-3,3-diethyl-2-methoxy-1,2,3,4-tetrahydropyridine-4-carboxamides **IIa** and **IIb** (Scheme 1).

Scheme 1.



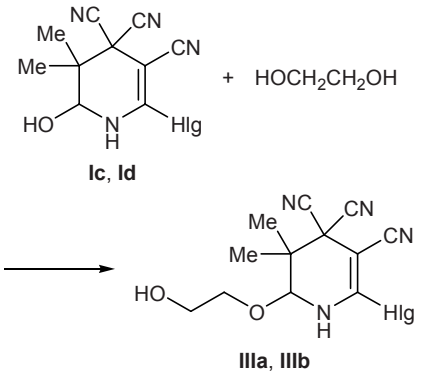
Ia, **Ib** **IIa**, **IIb**

Hlg = Cl (**a**), Br (**b**).

The reactions of tetrahydropyridines **Ic** and **Id** with ethylene glycol required a longer time and resulted in replacement of the hydroxy group, whereas the cyano groups remained intact (Scheme 2). The yield of 2-halo-6-(2-hydroxyethoxy)-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitriles **IIIa** and **IIIb** was 62–64%. We presumed that in this case replacement of the hydroxy group is not accompanied by hydrolysis of cyano group owing to higher acidity of the hydroxy group in α-diols as compared to methanol (by an order of magnitude). In fact, the reactions of tetrahydropyridines **Ia**–**Ic** with methanol in the presence of concentrated sulfuric acid afforded 85–95% of 5,5-dialkyl-2-halo-6-methoxy-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitriles **IVa**–**IVc** (Scheme 3).

The structure of compounds **II**–**IV** was confirmed by the IR, ^{1}H NMR, and mass spectra. The molecular

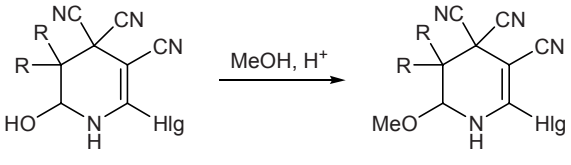
Scheme 2.



Ic, **Id** **IIIa**, **IIIb**

Ic, **IIIa**, Hlg = Cl (**a**); **Id**, **IIIb**, Hlg = Br (**b**).

Scheme 3.



Ia–Ic **IVa–IVc**

R = Et, Hlg = Cl (**a**), Br (**b**), R = Me, Hlg = Cl (**c**).

structure of **IIIa** and **IVb** was determined by X-ray analysis.

6-Chloro-4,5-dicyano-3,3-diethyl-2-methoxy-1,2,3,4-tetrahydropyridine-4-carboxamide (IIa). Methanol, 0.1 ml, was added to 0.066 g (0.25 mmol) of 2-chloro-5,5-diethyl-6-hydroxy-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (**Ia**) in 0.5 ml of anhydrous acetonitrile. After 2 h, the precipitate was filtered off and washed with acetone. An additional small amount of the product way be isolated by diluting the reaction mixture with water. Yield 0.066 g (85%), mp 194–195°C. IR spectrum, ν, cm^{-1}: 3380, 3250 (NH, NH_2); 2250, 2210 (C≡N); 1685 (C=O). ^1H NMR spectrum, δ, ppm: 0.90 t and 1.08 t (3H each, Me), 1.25 m and 1.50 m (1H each, C**H**$_2$CH$_3$), 1.80 m (2H, C**H**$_2$CH$_3$), 3.30 s (3H, OMe), 4.18 d (1H, 2-H), 7.42 s and 7.58 s (1H each, NH_2), 9.50 d (1H, NH). Mass spectrum: *m*/*z* 296 (I_{rel} = 0.2%). Found, %: C 52.60; H 5.81; N 18.85. $C_{13}H_{17}ClN_4O_2$. Calculated, %: C 52.62; H 5.77; N 18.88.

6-Bromo-4,5-dicyano-3,3-diethyl-2-methoxy-1,2,3,4-tetrahydropyridine-4-carboxamide (IIb) was obtained in a similar way from compound **Ib**. Yield 0.080 g (94%), mp 194–195°C. IR spectrum, ν, cm^{-1}: 3380, 3250 (NH, NH_2); 2250, 2210 (C≡N); 1685 (C=O). ^1H NMR spectrum, δ, ppm: 0.90 t (3H, Me), 1.08 t (3H, Me), 1.25 m and 1.50 m (1H each, C**H**$_2$CH$_3$), 1.80 m (2H, C**H**$_2$CH$_3$), 3.30 s (3H, OMe), 4.20 d (1H, 2-H), 7.30 s and 7.45 s (1H each, NH_2), 9.45 d (1H, NH). Mass spectrum: *m*/*z* 342/340 (I_{rel} = 10%) $[M]^+$. Found, %: C 45.71; H 5.09; N 16.36. $C_{13}H_{17}BrN_4O_2$. Calculated, %: C 45.76; H 5.02; N 16.42.

2-Chloro-6-(2-hydroxyethoxy)-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (IIIa). A solution of 0.118 g (0.5 mmol) of 2-chloro-6-hydroxy-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (**Ic**) in 0.3 ml of ethylene glycol was kept for 24 h. The precipitate was filtered off and washed with acetone. Yield 0.087 g (62%), mp 225–226°C. IR spectrum, ν, cm^{-1}: 3500, 3250 (OH, NH); 2260, 2220 (C≡N). Mass spectrum: *m*/*z* 280 (I_{rel} = 1%) $[M]^+$. Found, %: C 51.37; H 4.62; N 19.92. $C_{12}H_{13}ClN_4O_2$. Calculated, %: C 51.34; H 4.67; N 19.96.

2-Bromo-6-(2-hydroxyethoxy)-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (IIIb) was synthesized in a similar way from compound **Id.** Yield 0.1 g (64%), mp 210–211°C. IR spectrum, ν, cm^{-1}: 3520, 3250 (OH, NH); 2260, 2220 (C≡N). ^1H NMR spectrum, δ, ppm: 10.05 d (1H, NH), 4.61 d (1H, 2-H), 4.5 t (1H, OH), 3.6 m (1H, OC**H**$_2$CH$_2$O), 3.5 m (3H, OCH$_2$CH$_2$O), 1.4 s and 1.1 s (3H each, Me). Mass spectrum: *m*/*z* 326 (I_{rel} = 5%) $[M]^+$ (^{80}Br). Found, %: C 44.34; H 4.13; N 17.20. $C_{12}H_{13}BrN_4O_2$. Calculated, %: C 44.33; H 4.03; N 17.23.

2-Chloro-6-methoxy-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (IVc). Methanol, 0.1 ml, and one drop of concentrated sulfuric acid were added in succession to 0.118 g (0.5 mmol) of 2-chloro-6-hydroxy-5,5-dimethyl-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (**Ic**) in 0.5 ml of 1,4-dioxane. The mixture was kept for 24 h, and the precipitate was filtered off and washed with acetone. An additional amount of the product may be isolated by diluting the reaction mixture with water. Yield 0.1 g (85%), mp 208–209°C. IR spectrum, ν, cm^{-1}: 3250 (NH); 2251, 2211 (C≡N). ^1H NMR spectrum, δ, ppm: 1.1 s and 1.45 s (3H each, Me), 3.35 s (3H, OMe), 4.5 d (1H, 2-H), 10.3 d (1H, NH). Found, %: C 52.73; H 4.48; N 22.32. $C_{11}H_{11}ClN_4O$. Calculated, %: C 52.70; H 4.42; N 22.35.

Compounds **IVa** and **IVb** were synthesized in a similar way from nitriles **Ia** and **Ib**, respectively.

2-Chloro-5,5-diethyl-6-methoxy-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (IVa). Yield 0.13 g (94%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 3260 (NH); 2260, 2220 (C≡N). ^1H NMR spectrum, δ, ppm: 0.92 t and 1.08 t (3H each, CH$_2$C**H**$_3$); 1.3 m and 1.77 m, 1.9 m, and 2.08 m (1H each, C**H**$_2$CH$_3$); 3.35 s (3H, OMe); 4.5 d (1H, 2-H); 10.3 d (1H, NH). Mass spectrum: *m*/*z* 278 (I_{rel} = 10%) $[M]^+$. Found, %: C 56.11; H 5.46; N 20.07. $C_{13}H_{15}ClN_4O$. Calculated, %: C 56.02; H 5.42; N 20.10.

2-Bromo-5,5-diethyl-6-methoxy-1,4,5,6-tetrahydropyridine-3,4,4-tricarbonitrile (IVb). Yield 0.15 g (95%), mp 205–206°C. IR spectrum, ν, cm^{-1}: 3245 (NH); 2260, 2220 (C≡N). ^1H NMR spectrum, δ, ppm: 0.92 t and 1.07 t (3H each, CH$_2$C**H**$_3$); 1.25 m, 1.75 m, 1.87 m, and 2.02 m (1H each, C**H**$_2$CH$_3$); 3.32 s (3H, OMe); 4.4 d (1H, 2-H); 10.2 d (1H, NH). Mass spectrum: *m*/*z* 322 (I_{rel} = 8%) $[M]^+$. Found, %: C 48.27; H 4.64; N 17.38. $C_{13}H_{15}BrN_4O$. Calculated, %: C 48.31; H 4.68; N 17.34.

The IR spectra were recorded on an FSM 1202 instrument from samples dispersed in mineral oil. The ^1H NMR spectra were measured on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS-50 spectrometer. Single crystals of **IIIa** and **IVb** were examined using

an Enraf–Nonius CAD-4 four-circle automatic diffractometer (CuK_α-irradiation, graphite monochromator, ω scanning).

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